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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,431	03/25/2005	Gregoire Prevost	117P/PCT2/US	6671

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,431	PREVOST ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,26,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,26,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted August 27, 2008 wherein the rejections of record in the previous office action are traversed. This application is a national stage application of PCT/IB03/04922, filed September 27, 2002, which claims benefit of provisional application 60/414103, field September 27, 2002.

Claims 17-19, 26,31, and 32 are pending in this application.

Claims 17-19, 26, 31, and 32 as amended are examined on the merits herein.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (PCT international publication WO00/39130, of record in the previous office action) in view of Rybak. (PCT international publication WO01/64197, of record in the previous office action)

Gordon et al. discloses a pharmaceutical composition comprising one of a variety of compounds having an identical formula to formula (I) recited in instant claim 2. (pp. 2-9) Further specifically recited embodiments include the farnesyl transferase inhibitors of

instant claims 3-17. (pp. 17-27) These compounds are disclosed to possess anti-tumor activity (p. 16, lines 16-29) and to be useful for inhibiting prenyl transferases including farnesyl transferase. (p. 9, lines 8-25) Gordon et al. does not disclose a pharmaceutical composition comprising a combination of compound according to structure (I) and an anthracycline, or a method of treating nasopharyngeal cancer by administering such a composition to a subject. Gordon et al. also does not disclose a pharmaceutical kit comprising such a composition according to instant claims 34 and 38.

Rybak discloses therapeutic combinations of anthracyclines and farnesyl transferase inhibitors which are effective in the inhibition of tumor cell growth. (p. 13, lines 3-6) Preferred anthracycline derivatives include daunorubicin, doxorubicin, and idarubicin. (p. 21, lines 24-26) These compositions may be used in a method of inhibiting abnormal cell growth or treating various cancers having aberrant or mutated *ras* oncogene, (p. 22, lines 12-38) in a mammal, particularly a human. The two components may be administered either simultaneously or sequentially. (p. 23, lines 16-18)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a pharmaceutical composition comprising a farnesyl transferase inhibitor according to Gordon et al. and further comprising an anthracycline such as doxorubicin. One of ordinary skill in the art would have been motivated to combine the two components and to administer them to a patient suffering from cancer because both components were known to be useful for the treatment of cancer. One of ordinary skill in the art would have reasonably expected success because both compounds were

known to be useful for the same purpose. It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted August 27, 2008, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the cited references do not give any reason to single out this specific combination of the claimed inhibitor with an anthracycline. Applicants further claim that the large number of different compounds disclosed by Gordon et al. renders the claimed invention patentable. However, this is not the standard used in a judgment of obviousness. In order to render an invention obvious, the prior art does not need to explicitly disclose every element of the claim. Rather it merely needs to provide a motivation for practicing the claimed invention and a reasonable expectation of success in doing so. Furthermore in the decision of KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. ___, 82 USPQ2d 1385 (2007), the Supreme Court held that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

In the instant case, Gordon et al. does more than merely a out a laundry list of compounds. Instead, the reference discloses a general structural formula encompassing the claimed compound, thereby directing one of ordinary skill in the art

toward compounds having the same diazepine-imidazole structural core. Applicant then discloses 40 preferred examples all having very similar structures. This is hardly a laundry list. One of ordinary skill in the art could easily test all of these compounds for ras inhibition and anti-cancer activity.

As regards the combination of these compounds with anthracyclines, Rybak et al. provides a clear suggestion to combine farnesyl transferase inhibitors with anthracyclines. Since the farnesyl transferase inhibitors of Gordon et al. have the same effect (farnesyl transferase inhibition) as those explicitly disclosed by Rybak et al., one of ordinary skill in the art would have had a motivation to use them in the pharmaceutical compositions described by Rybak et al.

Furthermore there would be a reasonable expectation of success in combining the two components because the mere combination of two prior art drugs is routine in the art. Although, as Applicant points out, there have been certain well known cases of adverse or antagonistic reactions between therapeutic agents in combination therapy, one of ordinary skill in the art would know the be on the lookout for these interactions in patients receiving two or more drugs, and would not consider this to be a fatal flaw in any combination therapy. Still further, combination therapy is the standard in the treatment of cancer, and administering multiple known drugs is commonly practiced by those of ordinary skill in the art.

Applicants point to figure 2 in the disclosure as evidence of unexpected results for the claimed invention. However figure 2 merely discloses that the combination of the claimed compound and doxorubicin is more effective against cancer than doxorubicin

alone. There is no reason to believe that this is more than merely an additive effect, which would be expected in view of the fact that the two compounds are known to be useful individually. Furthermore the prior art already suggests the combination of a farnesyl transferase inhibitor with an anthracyclines as described by Rybak et al. The difference between the claimed invention and the prior art concerns the use of specific farnesyl transferase inhibitors. Therefore a finding of unexpected results would have to show not that the combination is more effective than doxorubicin alone, but that it is more effective than combinations incorporating the farnesyl transferase inhibitors of Rybak et al.

As regards Applicant's submission of documents relating to the failure of a combination of simvastatin and ezetimibe to produce additive results in the inhibition of atherosclerotic plaques, it is true that in some cases there is unexpected antagonism between two drugs when administered in combination for an indication against which they are both known to be useful individually. However, the overall expectation is that these cases are the exception rather than the rule and that two compounds useful for the same purpose will display additive effects when coadministered. This is especially the case in an art such as cancer chemotherapy where multiple drugs are routinely coadministered to produce additive effects.

For these reasons the rejection is maintained and made **FINAL**.

Claims 22, 26, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (PCT international publication WO00/39130, of record

in the previous office action) in view of Rybak. (PCT international publication WO01/64197, of record in the previous office action) as applied to claims 17-19 above, and further in view of Porter et al. (Reference of record in previous action)

The disclosure of Gordon et al. in view of Rybak is discussed above. Gordon et al. in view of Rybak does not disclose a method of treating nasopharyngeal carcinoma in particular.

Porter et al. discloses a study of the expression of certain oncogenes in nasopharyngeal carcinoma. (p. 105, left column, paragraphs 2-3) 73% of nasopharyngeal carcnomas studies were seen to have moderate or intense *ras* expression. (p. 106, right column, table I)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the compositions and methods of Gordon et al. in view of Rybak to treat nasopharyngeal carcinomas such as those of Porter et al. that express the *ras* oncogene. One of ordinary skill in the art would have been motivated to treat these cancers because Rybak already discloses that the combination of a FT inhibitor and an anthracycline is useful for treating cancers that express the *ras* oncogene, and Porter et al. discloses that many nasopharyngeal carcinomas fall within this category. One of ordinary skill in the art would reasonably have expected success because testing a tumor to determine whether a particular oncogene is expressed is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted August 27, 2008, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to the above ground of rejection in view of Gordon et al. and Rybak et al. alone.

Applicant further argues that the prior art does not disclose that farnesyl transferase inhibitors work in synergy with anthracyclines. However, a showing of obviousness does not require synergism but merely an additive effect. Applicant has shown no actual evidence of an unexpected synergistic result.

Applicant also argues that the cited references fail to teach that anthracyclines act via a ras-mediated pathway. However, Rybak et al. does teach anthracycline-containing compositions and discloses that they are useful for treating ras-containing tumors. This is sufficient disclosure to motivate one of ordinary skill in the art to use a composition containing an anthracycline and a farnesyl transferase inhibitor to treat any specific ras-expressing tumor, for example a ras-expressing nasopharyngeal carcinoma as described by Porter et al.

For these reasons the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
12/18/2008

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623